

Claims

1. A pharmaceutical composition comprising a nucleic acid molecule
5 encoding Saposin-related or a homologue thereof or a polypeptide encoded thereby or a fragment or a variant of said nucleic acid molecule or said polypeptide or an effector of said nucleic acid molecule or said polypeptide, preferably together with pharmaceutically acceptable carriers and diluents.
- 10 2. The composition of claim 1, wherein the nucleic acid molecule is a vertebrate or insect Saposin-related nucleic acid, particularly encoding the human homologs (such as human prosaposin (PSAP), human pulmonary surfactant-associated protein B (SFTPB), or human
15 hypothetical protein FLJ40379), and/or a nucleic molecule which is complementary thereto or a fragment thereof or a variant thereof.
3. The composition of claim 1 or 2, wherein said nucleic acid molecule is selected from the group consisting of
 - 20 (a) a nucleic acid molecule encoding a polypeptide as shown in SEQ ID NO: 2, 4, and/or 6, or an isoform, fragment or variant of the polypeptide as shown in SEQ ID NO: 2, 4, and/or 6 and/or a nucleic acid molecule complementary thereto;
 - (b) a nucleic acid molecule which comprises or is the nucleic acid
25 molecule as shown in SEQ ID NO: 1, 3, and/or 5 and/or a nucleic acid molecule complementary thereto;
 - (c) a nucleic acid molecule being degenerate with as a result of the genetic code to the nucleic acid sequences as defined in (a) or (b),
 - 30 (d) a nucleic acid molecule that hybridizes at 50°C in a solution containing 1 x SSC and 0.1% SDS to a nucleic acid molecule as defined in claim 2 or as defined in (a) to (c) and/or a nucleic acid molecule which is complementary thereto;

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- (e) a nucleic acid molecule that encodes a polypeptide which is at least 85%, preferably at least 90%, more preferably at least 95%, more preferably at least 98% and up to 99,6% identical to the human PSAP, SFTPb, and/or FLJ40379, as defined in claim 2 or to a polypeptide as defined in (a);
- (f) a nucleic acid molecule that differs from the nucleic acid molecule of (a) to (e) by mutation and wherein said mutation causes an alteration, deletion, duplication or premature stop in the encoded polypeptide.
4. The composition of any one of claims 1-3, wherein the nucleic acid molecule is a DNA molecule, particularly a cDNA or a genomic DNA.
5. The composition of any one of claims 1-4, wherein said nucleic acid encodes a polypeptide contributing to regulating the energy homeostasis and/or the metabolism of triglycerides.
6. The composition of any one of claims 1-5, wherein said nucleic acid molecule is a recombinant nucleic acid molecule.
7. The composition of any one of claims 1-6, wherein the nucleic acid molecule is a vector, particularly an expression vector.
8. The composition of any one of claims 1-5, wherein the polypeptide is a recombinant polypeptide.
9. The composition of claim 8, wherein said recombinant polypeptide is a fusion polypeptide.
10. The composition of any one of claims 1-7, wherein said nucleic acid molecule is selected from hybridization probes, primers and anti-sense oligonucleotides.

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11. The composition of any one of claims 1-10 which is a diagnostic composition.
- 5 12. The composition of any one of claims 1-10 which is a therapeutic composition.
- 10 13. The composition of any one of claims 1-12 for the manufacture of an agent for detecting and/or verifying, for the treatment, alleviation and/or prevention of metabolic diseases or dysfunctions, for example, but not limited to, metabolic syndrome, obesity, diabetes mellitus, eating disorder, cachexia, hypertension, coronary heart disease, hypercholesterolemia (dyslipidemia), and/or gallstones, and others, in cells, cell masses, organs and/or subjects.
- 15 14. The composition of any one of claims 1-13 for the manufacture of an agent for the modulation of pancreatic development.
- 20 15. The composition of any one of claims 1-14 for the manufacture of an agent for the regeneration of pancreatic tissues or cells, particularly pancreatic beta cells.
- 25 16. The composition of any one of claims 1-15 for application in vivo.
17. The composition of any one of claims 1-15 for application in vitro.
- 30 18. Use of a nucleic acid molecule encoding Saposin-related or a homologue thereof or a polypeptide encoded thereby or a fragment or a variant of said nucleic acid molecule or said polypeptide or an effector of said nucleic or polypeptide for controlling the function of a gene and/or a gene product which is influenced and/or modified by a Saposin-related homologous polypeptide.

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19. Use of a nucleic acid molecule encoding Saposin-related or a
homologue thereof or use of a polypeptide encoded thereby, or use of a
fragment or a variant of said nucleic acid molecule or said polypeptide,
or use of an effector of said nucleic acid molecule or said polypeptide
5 for identifying substances capable of interacting with a Saposin-related
homologous polypeptide.
20. A non-human transgenic animal exhibiting a modified expression of a
Saposin-related homologous polypeptide.
- 10 21. The animal of claim 20, wherein the expression of the Saposin-related
homologous polypeptide is increased and/or reduced.
22. A recombinant host cell exhibiting a modified expression of a
15 Saposin-related homologous polypeptide, or a recombinant host cell
which comprises a nucleic acid molecule as defined in any one of
claims 1 to 6.
23. The cell of claim 22 which is a human cell.
- 20 24. A method of identifying a (poly)peptide involved in the regulation of
energy homeostasis and/or metabolism of triglycerides in a mammal
comprising the steps of
- 25 (a) contacting a collection of (poly)peptides with a Saposin-related
homologous polypeptide or a fragment thereof under conditions
that allow binding of said (poly)peptides;
- (b) removing (poly)peptides which do not bind and
- (c) identifying (poly)peptides that bind to said Saposin-related
homologous polypeptide.
- 30 25. A method of screening for an agent which modulates the interaction of a
Saposin-related homologous polypeptide with a binding target/agent,
comprising the steps of

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- (a) incubating a mixture comprising
- (aa) a Saposin-related homologous polypeptide or a fragment thereof;
 - (ab) a binding target/agent of said Saposin-related homologous polypeptide or fragment thereof; and
 - (ac) a candidate agent
- under conditions whereby said Saposin-related homologous polypeptide or fragment thereof specifically binds to said binding target/agent at a reference affinity;
- (b) detecting the binding affinity of said Saposin-related homologous polypeptide or fragment thereof to said binding target to determine a (candidate) agent-biased affinity; and
- (c) determining a difference between (candidate) agent-biased affinity and reference affinity.

26. A method for screening for an agent, which modulates the activity of a Saposin-related homologous polypeptide, comprising the steps of

- (a) incubating a mixture comprising
- (aa) a Saposin-related homologous polypeptide or a fragment thereof; and
 - (ab) a candidate agent
- under conditions whereby said Saposin-related homologous polypeptide or fragment thereof exhibits a reference activity,
- (b) detecting the activity of said Saposin-related homologous polypeptide or fragment thereof to determine a (candidate) agent-biased activity; and
- (c) determining a difference between (candidate) agent-biased activity and reference activity.

27. A method of producing a composition comprising the (poly)peptide identified by the method of claim 24 or the agent identified by the method of claim 25 or 26 with a pharmaceutically acceptable carrier, diluent and/or adjuvant.

28. The method of claim 27 wherein said composition is a pharmaceutical composition for preventing, alleviating or treating of diseases and disorders, including metabolic diseases or dysfunctions, for example, but not limited to, such as metabolic syndrome, obesity, diabetes mellitus, eating disorder, cachexia, hypertension, coronary heart disease, hyper-cholesterolemia (dyslipidemia), and/or gallstones, and other diseases and disorders.
29. Use of a (poly)peptide as identified by the method of claim 24 or of an agent as identified by the method of claim 25 or 26 for the preparation of a pharmaceutical composition for the treatment, alleviation and/or prevention of diseases and disorders, including metabolic diseases or dysfunctions, for example, but not limited to, metabolic syndrome, obesity, diabetes mellitus, eating disorder, cachexia, hypertension, coronary heart disease, hyper-cholesterolemia (dyslipidemia), and/or gallstones, and other diseases and disorders.
30. Use of a nucleic acid molecule as defined in any one of claims 1 to 6 or 10, use of a polypeptide as defined in any one of claims 1 to 6, 8 or 9, use of a vector as defined in claim 7, use of a host cell as defined in claim 22 or 23 for the preparation of a pharmaceutical composition for the treatment, alleviation and/or prevention of diseases and disorders, including metabolic diseases or dysfunctions, for example, but not limited to, metabolic syndrome, obesity, diabetes mellitus, eating disorder, cachexia, hypertension, coronary heart disease, hypercholesterolemia (dyslipidemia), and/or gallstones, and other diseases and disorders.
31. Use of a nucleic acid molecule encoding Saposin-related or a homologue or a fragment thereof for the preparation of a non-human animal which over- or under-expresses the PSAP, SFTPB, and/or

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FLJ40379 gene product.

32. Kit comprising at least one of
- (a) a Saposin-related or a homologue nucleic acid molecule or a fragment or an isoform thereof;
 - (b) a Saposin-related or homologous amino acid molecule or a fragment or an isoform thereof;
 - (c) a vector comprising the nucleic acid of (a);
 - (d) a host cell comprising the nucleic acid of (a) or the vector of (b);
 - (e) a polypeptide encoded by the nucleic acid of (a), expressed by the vector of (c) or the host cell of (a);
 - (f) a fusion polypeptide encoded by the nucleic acid of (a);
 - (g) an antibody, an aptamer or another effector against the nucleic acid of (a) or the polypeptide of (b) , (e) , or (f) and /or
 - (h) an anti-sense oligonucleotide of the nucleic acid of (a).
33. Use of a saposin-related product and/or a modulator/effector thereof for the manufacture of a medicament to stimulate and/or induce the differentiation of insulin producing cells from progenitor cells.
34. The use of claim 33, wherein the progenitor cells are stem cells, preferably embryonic or somatic stem cells.
35. The use of any one of claims 33-34, wherein the stem cells are of mammalian origin, preferably of human origin.
36. The use of any one of claims 33-35, wherein the progenitor cells have been transfected with a pancreatic gene, particularly the Pax4 gene.
37. The use of a saposin-related product and/or a modulator/effector thereof for the manufacture of a medicament to promote the protection, survival and/or regeneration of insulin producing cells.

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38. The use of claim 37, wherein the insulin producing cells are beta-cells.

39. The use of claim 37 or 38, wherein the insulin producing cells are of mammalian origin, preferably of human origin.

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40. The use of any one of claims 37-39, wherein the insulin producing cells have been transfected with a pancreatic gene, particularly the Pax4 gene.

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41. The use of any one of claims 33-40 for the prevention or treatment of a disease going along with impaired beta-cell function, particularly for the treatment of beta-cell degeneration in patients suffering from diabetes type I, LADA, or progressed diabetes type II, or for the prevention of beta-cell degeneration in patients at risk to develop beta-cell degeneration, like for example but not limited to patients suffering from diabetes type I or II, or LADA in early stages.

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42. The use of any one of claims 33-41, wherein a saposin-related product or a modulator/effector thereof that influences the expression level or function of a saposin-related product is administered to a patient

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- (i) as a pharmaceutical composition e.g. enterally, parenterally or topically directly to the pancreas,
- (ii) via implantation of saposin-related protein product expressing cells, and/or
- (iii) via gene therapy.

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43. The use of claim 42, wherein the saposin-related product or modulator/effector thereof is administered in combination with another pharmaceutical composition useful to treat beta-cell degeneration, for example but not limited to hormones, growth factors, or immune modulating agents.

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44. The use of any one of claims 33-43, wherein the saposin-related product is a protein including purified natural, synthetic or recombinant saposin-related products and variants thereof.

5 45. The use of claim 44, wherein the saposin-related product is of mammalian origin, preferably human origin, more preferably selected from proteins or peptides substantially homologous to the human saposin-related precursor proteins as shown in Table 2.

10 46. The use of any one of claims 33-45, wherein the saposin-related product is a nucleic acid, e.g. RNA and/or DNA encoding a saposin-related protein product.

15 47. The use of any one of claims 33-46, wherein the differentiation of progenitor, e.g. stem cells into insulin-producing cells in vitro comprises
a) optionally activating one or more pancreatic genes in progenitor cells,
b) optionally aggregating said cells to form embryoid bodies,
c) cultivating said cells or embryoid bodies in specific differentiation
20 media containing saposin-related protein product and
d) identifying and optionally selecting insulin-producing cells.

25 48. The use of claim 47, wherein the saposin-related treated insulin producing cells are
(i) capable of a response to glucose and/or
(ii) capable of expressing glucagon.

30 49. The use of any one of claims 47-48, wherein the saposin-related insulin producing cells are capable of normalizing blood glucose levels after transplantation into mice.

50. The use of any one of claims 33-49, wherein an effective amount of in vitro saposin-related cells are transplanted to a patient in need.

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51. The use of any one of claims 33-50, comprising a stimulation of saposin-related expression,
wherein cells from a patient in need that have been modified to produce and secrete a saposin-related protein product in vitro are re-
5 implanted into the patient and/or
wherein cells of a patient in need are modified to produce and secrete a saposin-related protein product in vivo.

10 52. A method for differentiating or regenerating cells into functional pancreatic cells, the method comprising: (a) cultivating cells capable of being differentiated or regenerated into pancreatic cells in the presence of an effective amount of a saposin-related protein in vitro (b) allowing the cells to develop, to differentiate and/or to regenerate at least one pancreatic function; and (c) optionally preparing an effective amount of
15 the differentiated or regenerated pancreatic cells for transplantation into a patient in need thereof, particularly a human individual.

20 53. The method of claim 52, wherein the patient in need has (a) functionally impaired, (b) reduced numbers and/or (c) functionally impaired and reduced numbers of pancreatic cells.

54. The method of any one of claims 52-53, wherein said patient in need is a type I diabetic patient or type II diabetic patient or LADA patient.

25 55. The method of any one of claims 52-54, wherein the pancreatic cells are insulin-producing cells.

56. The method of any one of claims 52-55, wherein the pancreatic cells are beta-cells of the pancreatic islets.

30 57. The method of any one of claims 52-56, wherein the cells in step (a) are selected from embryonic stem cells, adult stem cells, or somatic stem cells.

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58. The method of any one of claims 52-57, wherein the cells in step (a) are of mammalian origin, preferably human origin.
- 5 59. The method of any one of claims 52-58, wherein the protein is added at concentrations between 1 ng/ml and 500 ng/ml, preferably between 10 and 100 ng/ml, more preferably at about 50 ng/ml.
- 10 60. The method of any one of claims 52-59, wherein the at least one pancreatic function is selected from insulin production in response to glucose and expression of glucagon.
- 15 61. A method for differentiating or regenerating cells into functional pancreatic cells, the method comprising: preparing an effective amount of a saposin-related product or of cells capable of expressing a saposin-related product for administration to a patient in need thereof.
- 20 62. The method of claim 61, wherein the saposin-related product is a protein or a nucleic acid.
63. The method of claim 61, wherein cells have been modified to produce and secrete a saposin-related protein product and are prepared for transplantation into a suitable location in the patient.
- 25 64. A cell preparation comprising saposin-related treated functional pancreatic cells obtainable by the method of any one of claims 52-60.
65. A cell preparation comprising a saposin-related product expressing cells obtainable by the method of any one of claims 61-63.
- 30 66. The preparation of claim 64 or 65, which is a pharmaceutical composition.

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67. The preparation of any one of claims 64-66 for the treatment or prevention of pancreatic diseases, particularly diabetes.

5 68. The preparation of any one of claims 64-67 for administration by transplantation or for use in a medical device.

69. The preparation of any one of claims 64-68, which contains pharmaceutically acceptable carriers, diluents, and/or additives.

10 70. The preparation of any one of claims 64-69, which is a diagnostic composition.

71. The preparation of any one of claims 64-69, which is a therapeutic composition.

15 72. The preparation of any one of claims 64-71 for the manufacture of an agent for the regeneration of pancreatic tissues or cells, particularly pancreatic beta cells.

20 73. The preparation of any one of claims 64-72 for application in vivo.

74. The preparation of any one of claims 64-72 for application in vitro.

25 75. A method for identifying and/or characterizing compounds capable of modulating the differentiation or regeneration of cells into functional pancreatic, particularly insulin-producing cells comprising:
contacting a compound to be tested with cells under conditions wherein the cells are capable of being differentiated or regenerated into functional pancreatic cells in the presence of a saposin-related protein
30 and determining the effect of the compound on the differentiation process.

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5 76. The method of claim 75 comprising transfecting the cells with a DNA construct containing a reporter gene under regulatory control of a gene involved in beta-cell differentiation, contacting said transfected cells with a compound to be tested and determining the activity of the reporter gene.

10 77. The method of claim 75 or 76 comprising contacting embryoid bodies which are cultivated in a differentiation medium enhancing beta-cell differentiation with a compound to be tested and determining differentiation into insulin-producing cells.

15 78. A method for identifying and/or characterizing compounds capable of modulating the differentiation or regeneration of cells into functional pancreatic, particularly insulin-producing cells comprising:
contacting a compound to be tested with cells under conditions wherein the cells are capable of being differentiated or regenerated into functional pancreatic cells and determining the effect of the compound on the expression of saposin-related protein.

20 79. Use of a preparation of saposin-related protein expressing cells for the treatment and prevention of diabetes.

25 80. The use of claim 79 for inducing the regeneration of pancreatic cells, particularly beta-cells of the islets.

81. Use of a preparation of saposin-related product treated cells for the treatment and/or prevention of diabetes.

30 82. The use of claim 81 wherein the cells are differentiated progenitor cells capable of insulin production.